AWARD NUMBER: W81XWH-15-1-0268

TITLE: Randomized Trial of Asprin as Adjuvant Therapy for Node-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Eric Winer

CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute
Boston, MA 02215

REPORT DATE: OCTOBER 2017

TYPE OF REPORT: ANNUAL

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	15 Sep 2016 - 14 Sep 2017

4. TITLE AND SUBTITLE

Randomized Trial of Asprin as Adjuvant Therapy for Node-Positive Breast Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0268

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Eric Winer
Wendy Chen

E-Mail: Eric_Winer@dfci.harvard.edu; Wendy_Chen@dfci.harvard.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Dana-Farber Cancer Institute

450 Brookline Avenue
Boston, MA 02215-5450

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

In the United States, more than 3 million women are living after a breast cancer diagnosis. There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. These would not only save thousands of lives, but offer improved quality of life for those who do not tolerate current treatments, and treatment options to women in developing countries who currently get none.
We will enroll 3000 women with node-positive HER2 negative Stage II or III breast cancer with a 1:1 randomization to aspirin 300 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We will exclude those at high risk of bleeding complications with aspirin (≥age 70, history of prior stroke, significant gastrointestinal bleeding, anticoagulation) or those with indications for taking aspirin (history of myocardial infarction or atrial fibrillation) Breast cancer advocates will be involved in the creation of all recruitment letters, consent forms, and information sheets. We would conduct the trial in a multi-center collaboration of the Brigham and Women's Hospital, Dana Farber Harvard Cancer Institute, and the Alliance for Clinical Trials in Oncology. The research infrastructure, long-standing leadership roles in clinical trials, and ability to rapidly accrue subjects make the assembled research team ideal to lead a US trial within the proposed time frame.

15. SUBJECT TERMS
Breast cancer, adjuvant treatment, aspirin, randomized controlled trial

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	16	19b. TELEPHONE NUMBER *(include area code)*

ABSTRACT

In the United States, more than 3 million women are living after a breast cancer diagnosis. There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. These would not only save thousands of lives, but offer improved quality of life for those who do not tolerate current treatments, and treatment options to women in developing countries who currently get none.

We will enroll 2936 women with node-positive HER2 negative Stage II or III breast cancer with a 1:1 randomization to aspirin 325 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We will exclude those at high risk of bleeding complications with aspirin (>age 70, history of prior stroke, significant gastrointestinal bleeding, anticoagulation) or those with indications for taking aspirin (history of myocardial infarction or atrial fibrillation) Breast cancer advocates will be involved in the creation of all recruitment letters, consent forms, and information sheets. We would conduct the trial in a multi-center collaboration of the Brigham and Women's Hospital, Dana Farber Harvard Cancer Institute, and the Alliance for Clinical Trials in Oncology. The research infrastructure, long-standing leadership roles in clinical trials, and ability to rapidly accrue subjects make the assembled research team ideal to lead a US trial within the proposed time frame.

TABLE OF CONTENTS

Page No.

1. INTRODUCTION:

There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. We believe aspirin holds great promise, and propose a randomized controlled trial to test that promise. There is compelling epidemiologic, in-vitro, and in-vivo, evidence of aspirin's potential. We will enroll 2936 women with node-positive Stage II or III breast cancer with a 1:1 randomization to aspirin 300 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We hypothesize that breast cancer survivors randomized to aspirin will have fewer recurrences and longer recurrence-free survival than those on placebo.

2. KEYWORDS:

Breast cancer, adjuvant treatment, aspirin, randomized controlled trial

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The goals and milestones listed below pertain to months 12-24 in the approved SOW:

Specific Aims 1 & 2: Clincal Trial

- Screen subjects and consent eligible subjects to study (months 6-30) – Began December 2016, ongoing
- Assign participants to one of two randomized groups study (months 6-30) – Began December 2016, ongoing
- Distribute study medication for the first 6 months study (months 6-30) – Began December 2016, ongoing
- Review accrual statistics to ensure that accrual goals will be met (every 6 months) – This is actually done every month. Began December 2016 and occurs on weekly basis
- Assess participants every 6 months while on study (months 12-30) – Began December 2016, ongoing
- Assess for toxicity and adverse events (ongoing) – Began December 2016, ongoing
- Assess for need for dose reduction (ongoing) – Began December 2016, ongoing
- Assess for need for proton pump inhibitor (ongoing) – Began December 2016, ongoing
- Assess compliance with study drug (months 12-60) Began December 2016, ongoing
- Coordinate with sites and data for data collection (months 6-60) – Began December 2016, ongoing

Specific Aim 3: Creation of biospecimen and epidemiologic biobank

- Collection of tumor specimens at baseline (months 6-30) – Began December 2016, ongoing
- Collection of blood and urine specimens at baseline (months 6-30) – Began December 2016, ongoing
- Storage and cataloguing of specimens (months 6-60) – Began December 2016, ongoing
- Collection of covariate data on sleep, stress, BMI, etc. (months 6-60) – Began December 2016, ongoing

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Referring to the SOW:

Specific Aims 1 & 2: Clinical Trial

- We began enrollment on Dec. 8, 2016. This included screening, randomization, distribution of study medication, collection of biospecimens, collection of epidemiologic data, collection of information on toxicity and adverse events, need for dose reduction, and need for proton pump inhibitor.
- We have assessed enrollment monthly
- As of August 31, 2017, 1020 have been approved to enroll subjects, training of staff and local IRB approval is ongoing at those sites
- As of October 2, 2017 197 have registered and randomized

Specific Aim 3: Biorepository

- As of September 27, 2017, 69% have submitted a biospecimen (blood and/or tumor) and 83% a lifestyle questionnaire

Additional Achievement, not in the SOW

- The first External Advisory Board meeting was held 11/21/16 . A trials in progress poster was presented at the semi-annual Alliance for Clinical Trials Oncology meeting in May 2017 at the annual American Society for Clinical Oncology meeting in June 2017. Our Patient Advocates publicized the study at the National Advocate Leadership Summit for the National Breast Cancer Coalition in May 2017.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will continue to enroll and randomize subjects. The study is still being opened and undergoing local IRB approval at multiple sites across the country so the enrollment rate is estimated to increase greatly over the next few months.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Our patient accrual is slightly behind what we had anticipated by this time. . Since we also received additional funding through the National Cancer Institute (NCI) to help with accrual and the also utilized the NCI central IRB, the study was not activated by the NCI until December 2016. Even after NCI central IRB approval, the individual sites will also have their own steps for local IRB approval and protocol activation, a process that can take over 6 months. However we are encouraged by the fact that 1020 sites have registered to enroll patients indicating of the strong enthusiasm for this trial in the oncologic community. It is unlikely that a site would open a protocol unless they were planning on enrolling subjects. The current trajectory for enrollment is similar to that for other cooperative group studies. Similar to those studies, we anticipate that accrual will be approximately 100 subjects per month. As of our last full months of accrual, we were at 40 subjects per month.

Furthermore, the study is also open in the other cooperative groups including ECOG, SWOG, and CCTG. Health Canada is also considering opening the study. The study is promoted at all of the cooperative group meetings and we have also engaged our advocates and their network to improve accrual
In addition, the trial is presented on the monthly Alliance breast conference calls and the biannual meetings. The study will also be presented at a monthly NCI Community Oncology Research program webinar soon since many community sites have enrolled subjects.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

A major cost of the trial is the $1400 per patient enrollment fee paid to the Alliance. As we have just started paying these fees, these expenditures are lower than expected. We expect to catch up with patient enrollment (and expenditures) in coming years.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.
Significant changes in use or care of human subjects

An update was submitted in August 2017 to NCI and NCI central IRB for several minor amendments to the protocol to increase accrual. This update was approved fully by the NCI central IRB on September 6, 2017 and approved with minor recommendations by the NCI on September 6, 2017. The main changes made to increase accrual were 1) to change the washout period after end or radiation/chemotherapy from 60 to 30 days, 2) to change the time from one year to 30 days that a subject needed to stop regular aspirin use prior to enrolling, 3) allow a +/- 14 day window for the 6 month visit, 4) allow high risk node negative (defined as T2-T4/N0) triple negative patients to enroll. None of these change impacted the risk/benefit ratio to subjects nor the statistical plan.

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations
Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year*

(international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Chen WY, Winer EP, Barry WT, Hudis CA, Openshaw TH, Visvanathan K, Symington B, Matyka C**,** Holmes MD**.** ABC trial (AO11502) A randomized phase III double blinded placebo controlled trial of aspirin as adjuvant therapy for node positive breast cancer. (Abstract585). 2017 Annual meeting of the American Society for Clinical Oncology.

- **Website(s) or other Internet site(s)**
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

http://abctrial.org/
This is the website for general information about the trial, for interested patients and clinicians. There are no results to disseminate yet.

- **Technologies or techniques**
Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name: Eric Winer
Role: Principal Investigaor
1.20 calendar months
Contribution: Dr. Winer has had multiple meetings and conference calls with both the National Cancer Institute and Alliance for Clinical Trials in Oncology to secure approval for the protocol at both the NCI and Alliance. He has provided key input on the protocol and study design and has been a key liaison across the partnering organizations.

Name: Wendy Chen
Role: Co-Investigator
1.80 calendar months
Contribution: Dr. Chen serves as study chair for the clinical trial at the Alliance for Clinical Trials in Oncology so has been in charge of writing and revising the protocol and securing approval through the Alliance and NCI. She has also been participating in regular conference calls on protocol revisions and approval.

Name: William Barry
Role: Biostatistician
0.6 calendar months
Contribution: Dr. Barry has helped to write the statistical analysis parts of the protocol and has also provided key input on study design. He has also participated in multiple conference calls to address questions about statistical issues relevant to the study. Contribution to project: Dr. Watson provided details for the biospeciman repository collection for the protocol and he provided input into the protocol design

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Bayer Pharma AG, Mullerstr 178, 13353 Berlin, Germany is supplying both aspirin and placebo for this trial at no cost to the trial. We have executed a contract with them to do so on May 13, 2016.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A